Use of trastuzumab for HER2-positive metastatic breast cancer in daily practice: a population-based study focusing on the elderly

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The addition of trastuzumab to chemotherapy in human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) prolongs overall survival (OS) in clinical trials. However, treatment patterns and survival in daily practice are unknown. This study aims to compare trastuzumab use and outcome in HER2-positive MBC patients in a population-based cohort with clinical trial cohorts, with a special focus on elderly patients. MBC patients treated with trastuzumab-based chemotherapy in north-east Netherlands between 2005 and 2009 were identified from 23 hospital pharmacies and the Netherlands Cancer Registry. Baseline, treatment, and survival characteristics (Kaplan–Meier analysis) were compared with those found in clinical trials and differences in patients aged less than 65 versus 65 years or more were studied. Of 225 HER2-positive MBC patients (median: 54.8 years), 130 were treated with first-line trastuzumab. In first-line treatment, the median treatment duration was 9 months and the median OS was 30.7 months, which is comparable with the OS of 31.2 months found in a clinical trial with comparable baseline characteristics. In 25 patients aged 65 years or more compared with those aged less than 65 years treated with first-line trastuzumab, patients with a history of early breast cancer had less often been treated with adjuvant chemotherapy (36 vs. 71%; $P = 0.001$). Other baseline characteristics and OS were similar. Patient, treatment, and survival characteristics in a HER2-positive MBC population-based cohort share considerable similarities to those found in clinical trials. The influence of age on trastuzumab treatment was not detected. ***Anti-Cancer Drugs*** **27:127–132 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Overexpression of the human epidermal growth factor receptor 2 (HER2) protein and/or amplification of the *HER2* gene in breast cancer is found in around 15–20% of patients [1,2]. Trastuzumab is a monoclonal antibody directed against HER2. In the pivotal trial of Slamon *et al.* [3], trastuzumab and paclitaxel versus paclitaxel alone in HER2-positive metastatic breast cancer (MBC) prolonged time to progression by 3.9 months, and increased the objective response rate by 24% and overall survival (OS) from 18.4 to 22.1 months. Single trastuzumab therapy as the first-line or second-line treatment in HER2-positive MBC resulted in response rates of 34 and 15%, respectively [4,5].

Trastuzumab was approved in 1998 by the US Food and Drug Administration and in 2000 by the European Medicines Agency (EMEA) for the treatment of HER2-positive MBC [6,7]. Indications were as follows: (i) first-line therapy in combination with paclitaxel when anthracycline-containing therapy was found to be contraindicated because of cardiotoxicity of the combination; (ii) as monotherapy for second-line or third-line therapy after failure of hormonal therapy. After approval, the national and international community adopted trastuzumab as a treatment option for HER2-positive MBC [8–10]. Trastuzumab was considered the first-line treatment in HER2-positive MBC, preferably in combination with paclitaxel or docetaxel [11–14]. Nowadays, additional effective but expensive treatment combinations such as pertuzumab or trastuzumab emtansine for HER2-positive MBC are available [15,16]. To define new treatment algorithms for HER2-positive MBC in all patient subgroups, accurate knowledge of treatment efficacy and side-effects of trastuzumab treatment in the general population is more necessary. Strikingly, even after more than 10 years of widespread use of trastuzumab in HER2-positive MBC, survival benefits in population-based samples have not been explored thoroughly. When clinical trials reflect outcome in daily practice, the implementation of expensive drugs in the patient group of everyday practice will be even more justified [17].

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The aim of this study is therefore to describe in a population-based cohort patient, tumor, treatment, and survival characteristics of HER2-positive MBC patients treated with trastuzumab. The results were compared with those reported in clinical trials with a special focus on elderly patients.

Patients and methods

Study population

Patients diagnosed with HER2-positive MBC and treated with trastuzumab between 2005 and 2009 in the north-eastern region of the Netherlands (population 3.3 million) were included. Details of the selection have been provided elsewhere [18]. In summary, patients were selected by investigation of the 23 regional hospital pharmacies records and cross-checked with the population-based data from the nationwide population-based the Netherlands Cancer Registry, which is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). TNM classification was used for the staging. Follow-up was completed up to January 2014.

Guideline recommendation in the period studied

The Dutch national guideline for the diagnosis and treatment of breast cancer in 2004 suggested trastuzumab (3-weekly regimen with an 8 mg/kg loading dose, followed by 6 mg/kg) with a taxane as first-line therapy in HER2-positive MBC, especially when patients had received anthracycline-containing adjuvant therapy [19, 20]. In 2008, the revised guideline recommended 12-weekly cycles of paclitaxel combined with trastuzumab until progression as first-line treatment for HER2-positive MBC [21]. It was advised to perform 3-monthly multigated acquisition scans and to withhold treatment in case of a 10% decrease in left ventricular ejection fraction or a left ventricular ejection fraction of less than 50%. Lapatinib was only recommended after the failure of trastuzumab-containing therapy.

Detailed data collection

Registration clerks of the Netherlands Cancer Registry gathered detailed information on patient and tumor characteristics as well as treatment information before, during, and after the start of trastuzumab-containing therapy. The quality of the data was ensured by thorough training and computerized consistency checks at regional and national levels. Coding of the items was performed according to international coding rules (IACR). Extensive information on treatment intervals and number of trastuzumab cycles was also collected. The reasons for discontinuation of trastuzumab-containing therapy and data on OS were recorded.

Comparison with clinical trials and prospective cohort study

Baseline, treatment, and survival characteristics were compared with the results from the final analysis of two randomized clinical trials (Table 4). In these trials, HER2-positive MBC patients were treated with trastuzumab and a taxane as first-line therapy [3,22]. A comparison was also made with the results from the subgroup of White patients entered into the prospective observational registHER cohort study, which included patients with HER2-positive MBC [23].

Statistical analyses

Patients who received trastuzumab were divided into two groups, namely, those who received it as first-line treatment for MBC or as subsequent (second line or later). The χ^2 and Fisher exact tests were used to compare patients and tumor characteristics between the two groups of trastuzumab treatment. Baseline patient and tumor characteristics included age, early breast cancer (EBC) and previous treatment for EBC, histology, grade, hormonal receptor status (positive estrogen and/or progesterone receptor vs. negative estrogen and progesterone receptor), type of surgery, and site of metastasis. Age was calculated at the start of trastuzumab treatment or the date of diagnosis of MBC in case of unknown starting date of trastuzumab. OS was calculated from the date when the diagnosis of MBC was recorded until the date of death by any cause. Patients with an unknown date of diagnosis of MBC were excluded from this analysis ($n=9$). In patients treated with first-line trastuzumab therapy, OS was also calculated from the start of trastuzumab treatment for comparison with trial results. Furthermore, baseline and survival characteristics in patients aged less than 65 versus 65 or more years were compared using the χ^2-test and the log-rank test, respectively. The statistical significance level was set at a P-value less than 0.05. Analyses were carried out using the STATA software package (version 13.1 for Windows; Stata Corporation LP, College Station, Texas, USA).

Results

A total of 225 MBC patients treated with trastuzumab were identified and included in this analysis. The 23 patients who had already been treated with trastuzumab in the adjuvant setting for early-stage breast cancer were excluded. For patient characteristics at the start of trastuzumab treatment, see Table 1. Trastuzumab was used as first-line therapy in 58% of patients (130/225 patients); these patients had more often previously been treated for EBC compared with patients presenting with metastatic disease (52 vs. 25%; $P<0.001$). In first-line therapy, trastuzumab was administered in 90% of patients, administered in combination with chemotherapy and in 7.7% as single-agent therapy (Table 2). The most frequently used combination was trastuzumab and paclitaxel, followed by the combination of trastuzumab and vinorelbine. The median follow-up duration since the start of trastuzumab treatment in first-line therapy for the patients who were alive was 72.1 months. The median OS of patients treated with first-line trastuzumab was

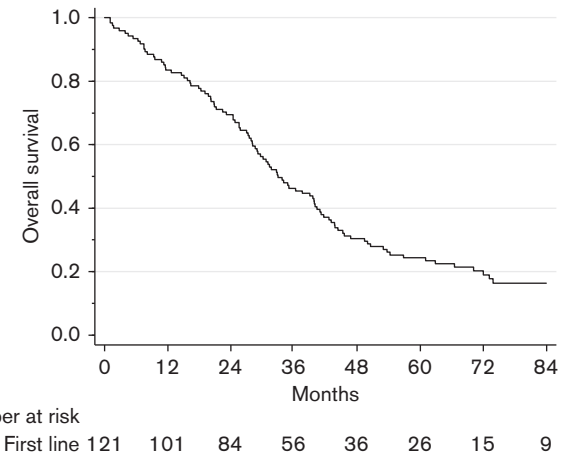
Table 1 Patient and tumor characteristics of the population at baseline treated with trastuzumab for HER2-positive metastatic breast cancer in north-east Netherlands between 2005 and 2009

	N (%)			
	All patients	Trastuzumab in first line	Trastuzumab in subsequent lines	*P*-value
Age				
Mean (range)	54.8 (25–91)	55.7 (31–91)	53.6 (25–76)	NS
<50	69 (31)	38 (29)	31 (33)	NS
50–64	110 (49)	63 (48)	47 (49)	
≥65	46 (20)	29 (22)	17 (18)	
Previous EBC				
Treated with CT	92 (41)	68 (52)	24 (25)	<0.001
Treated without CT	75 (33)	40 (31)	35 (37)	
No previous EBC	58 (26)	22 (17)	36 (38)	
Histology				
Ductal	211 (94)	121 (93)	90 (95)	NS
Lobular	11 (4.9)	6 (4.6)	5 (5.3)	
Other/unknown	3 (1.3)	3 (2.3)	0 (0.0)	
Grade				
1	7 (3.1)	3 (2.3)	4 (4.2)	0.031
2	54 (24)	34 (26)	20 (21)	
3	111 (49)	71 (55)	40 (42)	
Unknown	53 (24)	22 (17)	31 (33)	
Receptor status (ER or PR)				
Positive	123 (55)	65 (50)	58 (61)	NS
Negative	92 (41)	59 (45)	33 (35)	
Unknown	10 (4.4)	6 (4.6)	4 (4.2)	
Surgery				
Lumpectomy	60 (27)	37 (29)	23 (24)	0.003
Mastectomy	108 (48)	71 (55)	37 (39)	
No surgery	57 (25)	22 (17)	35 (37)	
Site of metastasis				
Breast	9 (4.0)	5 (3.8)	4 (4.2)	NS
Lymph node	37 (16)	23 (18)	14 (15)	NS
Lung	57 (25)	38 (29)	19 (20)	NS
Liver	92 (41)	46 (35)	46 (48)	0.049
Bone	100 (44)	58 (45)	42 (44)	NS
Skin	12 (5.3)	7 (5.4)	5 (5.3)	NS
CNS	9 (4.0)	6 (4.6)	3 (3.2)	NS
Other	19 (8.4)	12 (9.2)	7 (7.4)	NS
Total	225 (100)	130 (100)	95 (100)	

CNS, central nervous system; CT, chemotherapy; EBC, early breast cancer; ER, estrogen receptor; PR, progesterone receptor.

32.8 months (Fig. 1) and 30.7 months calculated from the start of trastuzumab treatment. The median trastuzumab treatment duration in patients treated with first-line trastuzumab-containing therapy was 9 months (quartile range: 3.8–15.5 months) and was discontinued in 32% because of progression, in 15% because of cardiotoxicity, and in 18.0% because of death (Table 3). Discontinuation because of cardiotoxicity occurred only in 16% of patients

Fig. 1



Kaplan–Meier analysis of overall survival in HER2-positive metastatic breast cancer patients treated with first-line trastuzumab therapy.

Table 3 Reasons for discontinuation of trastuzumab-containing therapy in HER2-positive metastatic breast cancer in north-east Netherlands between 2005 and 2009

	N (%)		
	All patients	Trastuzumab in first line	Trastuzumab in subsequent lines
Progression	62 (33)	36 (32)	26 (31)
Death	36 (19)	20 (18)	16 (19)
Cardiotoxicity	32 (16)	17 (15)	15 (18)
Number of trastuzumab cycles			
0–10	5 (16)	1 (6.0)	4 (27)
11–20	11 (34)	6 (35)	5 (33)
21–30	5 (16)	3 (18)	2 (13)
≥31	5 (16)	4 (24)	1 (7.0)
Unknown	6 (19)	3 (18)	3 (20)
Prior treatment with anthracycline	23 (72)	10 (59)	13 (87)
Toxicity	3 (1.5)	3 (2.7)	0 (0.0)
Reaching aimed therapy duration[a]	19 (9.9)	11 (9.9)	8 (9.5)
Patient refusal	1 (0.5)	0 (0.0)	1 (1.2)
Other	15 (7.7)	11 (9.9)	4 (4.8)
Unknown	27 (14)	13 (12)	14 (17)
Total	195 (100)	111 (100)	84 (100)

[a]Defined by the treating physician.

Table 2 Trastuzumab-containing treatment schedules for HER2-positive metastatic breast cancer in north-east Netherlands between 2005 and 2009

	N (%)		
	All patients	Trastuzumab in first line	Trastuzumab in subsequent lines
Trastuzumab monotherapy	18 (8.0)	10 (7.7)	8 (8.4)
Trastuzumab/paclitaxel, followed by trastuzumab monotherapy	144 (64)	74 (57)	70 (74)
Trastuzumab/vinorelbine	26 (12)	17 (13)	9 (9.5)
Trastuzumab/capecitabine	4 (1.8)	3 (2.3)	1 (1.1)
Trastuzumab/carboplatin/paclitaxel	8 (3.6)	8 (6.2)	0 (0.0)
Other	19 (9.3)	16 (12)	5 (5.3)
Unknown	4 (1.8)	2 (1.5)	2 (2.1)
Total	225 (100)	130 (100)	95 (100)

Table 4 Baseline and treatment characteristics of patients treated with trastuzumab as first-line therapy for metastatic breast cancer in our retrospective collected cohort, two clinical trials, and the prospective registHER cohort

	This analysis	H0648g trial	M77001 trial	RegistHER[a]
Inclusion time	2005–2009	1995–1997	2000–2002	2003–2006
Patients treated with first line trastuzumab (*n*)	130	92	92	793
Mean age (years)	56	51	53[b]	54[b]
Previous therapy with neoadjuvant CT for EBC (%)	52	97	71	73
ER or PR positivity (%)	50	–	41	54.7
Site of metastatic disease at diagnosis (%)				
Bone	45	–	34	–
Bone or bone + breast	–	–	–	14
Visceral	64	–	89	61
Lung	29	–	40	–
Liver	35	–	49	–
Locoregional	22	–		17
Skin	5.4	–		–
Any CNS	4.6	–	–	7.2
Other	9.2	–	60	0.3
Discontinuation because of cardiotoxicity (%)	15	13	17	–
Median PFS (months)	–	6.9	11.7	10.2
Median OS (months)	30.7	22.1	31.2	37.3[c]
Median TTF (months)	9.0[d]	5.8	–	–

CNS, central nervous system; CT, chemotherapy; EBC, early breast cancer; ER, estrogen receptor; OS, overall survival; PFS, progression-free survival; PR, progesterone receptor; TTF, time to treatment failure.
[a]Data shown for the subgroup of White patients.
[b]Median age.
[c]Calculated from the time of metastatic breast cancer diagnosis.
[d]Estimated using the median treatment duration.

in the first ten trastuzumab treatment cycles. Baseline and treatment characteristics of our population-based patient cohort were comparable with those reported in clinical trials (Table 4).

In first-line therapy, 29 patients were aged 65 years or more. Of these patients, 25 had a history of EBC and were less often treated with adjuvant chemotherapy compared with patients younger than 65 years (36 vs. 71%; $P = 0.001$), and had no further different baseline characteristics. The median OS in the patients aged 65 years or more treated with first-line trastuzumab was 29.6 months compared with 33.7 months in patients aged less than 65 years ($P = 0.139$). Treatment duration and discontinuation rates because of cardiotoxicity were equal.

Discussion

In this pattern-of-care study of 225 HER2-positive MBC patients, 130 patients were treated with first-line trastuzumab, with a median treatment duration of 9 months and a median OS of 30.7 months.

The baseline and treatment characteristics of our cohort share considerable similarities to the highly selected population of the M77001 randomized trial in which docetaxel was administered with or without trastuzumab in first-line MBC. OS in this trial is highly comparable to the OS that we found (31.2 vs. 30.7 months, respectively) [3,24]. The OS that we found was higher compared with the paclitaxel and trastuzumab arm in the H0648g trial (30.7 vs. 22.1 months). This could at least partly be explained by the required previous adjuvant anthracycline therapy (97 vs. 52% in our analysis) that patients received in the H0648g trial, implicating more aggressive disease when it recurred.

In the prospective observational US registHER study, 919 patients with HER2-positive MBC patients were entered between 2003 and 2006. Selection was performed by the treating physician and patients agreed to participate. This study indicated a 4.5-month higher median OS of 37.3 months in White patients calculated from MBC diagnosis compared with our analysis despite highly similar baseline characteristics such as age, tumor grade, and previous adjuvant chemotherapy [22]. As 90% of patients in the registHER had an Eastern Cooperative Oncology Group performance status of 0 or 1, selection bias likely occurred in contrast to our population-based analysis, contributing toward the gap in OS.

In our population-based sample, discontinuation of trastuzumab treatment because of cardiotoxicity was found in 16% of all patients. In this subgroup of patients, 72% of patients had been treated before with an anthracycline. As only 41% of patients in the total patient groups had been treated with chemotherapy, this indicates the known cardiotoxic effects of these agents [23,25]. Our discontinuation rate is comparable with that of the pivotal trials [3,24], particularly in case of prolonged administration of trastuzumab, most often after more than 10 cycles (Table 3) [26].

Although the national and international guidelines published in the period studied suggested the combination of trastuzumab with a taxane as first-line therapy in HER2-positive MBC, we found a modest compliance of 57% [12,27]. Other observational studies reported similar rates [28–31]. Possibly combining treatment with a

taxane was not preferred, given its toxicity profile, or because of the need for weekly intravenous therapy. As a substitute, vinorelbine with a more favorable toxicity profile has been combined with trastuzumab. Former randomized studies have also shown the efficacy of the trastuzumab–vinorelbine combination [32]. Addressing the demand for a less toxic combination, this combination was subsequently adopted as a possible treatment option in the latter national guideline [33].

In an era with increasing life expectancy, elderly patients with breast cancer represent an increasingly important subgroup. For example, over 50% of diagnosed breast cancer patients are aged more than 65 years and almost 35% are aged more than 75 years [data: Cancer Statistics from the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, *http://seer.cancer.gov*]. Unfortunately, this subgroup of patients is often under-represented in clinical trials. As only 22% of our patients treated with trastuzumab as first-line therapy were aged 65 years or more, the elderly are likely also under-represented in this analysis. With a comparable median age of patients participating in the clinical trials, the elderly were probably also under-represented in these trials (Table 4). This selection bias could reflect the reluctance to expose these patients to a potential (cardio) toxic and expensive treatment, particularly as during the period studied, trastuzumab was a relatively new treatment option. Patients aged 65 years or more were less often treated with adjuvant chemotherapy for previous EBC. However, evidence suggests that elderly patients may benefit from adjuvant chemotherapy to the same extent as younger patients [34]. The reduced rate of adjuvant treatment in the elderly could probably reflect the reluctance to start a toxic adjuvant treatment in the elderly with often comorbid disease and reduced functional capacity.

Of the patients included in our analysis, 95 out of 225 were treated with trastuzumab in subsequent lines for MBC. They constitute a selected population in which survival characteristics cannot be compared with patients treated in first line. The 2002 national guideline already suggested trastuzumab with a taxane as first-line therapy and in 2004 and 2005, the guidelines recommended this combination to be considered as first-line therapy [13,19, 20]. This indicates some reluctance to start a first-line trastuzumab-containing regime and to withhold an effective anthracycline-containing regime from patients. The EMEA warned in a public statement in 2001 that the use of anthracyclines after discontinuation of trastuzumab may carry a higher risk of cardiac toxicity [35]. Furthermore, even at the start of the studied period, there was an ongoing debate on the clinical impact of cardiotoxicity [36]. For EBC, the implementation of trastuzumab was studied between 2005 and January 2007 [37]. Ninety-four percent of HER2-positive EBC patients diagnosed between September 2005 and January 2007 who were treated with chemotherapy were also treated with trastuzumab. As of 2005, trastuzumab treatment for HER2-positive EBC was recommended in the Netherlands [20]. This suggests a great willingness to rapidly adopt new guideline recommendations and to use trastuzumab in a larger population.

We acknowledge some limitations of our analysis. As is almost inherent to all retrospective cohort studies focusing on daily practice, our data collection was slightly hampered by inconsistencies and sometimes lack of detailed patient, treatment, and survival characteristics. However, with intensive chart review, the data collection was maximized. Furthermore, using hospital pharmacy records for patient selection, we were able to maximize our inclusion of patients who had indeed received trastuzumab, minimizing selection bias. Our analysis also lacks progression-free survival data. Because of the retrospective cohort design of our analysis, we could not accurately determine progression-free survival. Furthermore, because of differences in time when response measurement was performed during treatment, there may have been an outcome bias. As a surrogate, we have measured the duration of treatment. It estimates time to treatment failure, a composite endpoint of progression, death, or discontinuation of treatment. Time to treatment failure found in one of the clinical trials was lower compared with our duration of treatment (Table 4). More frequent and extensive response evaluations in clinical trials compared with daily practice could explain this difference.

Considering all of the above, our population-based cohort shares great similarities with the previously conducted clinical trials with highly selected study populations. This indicates that treatment outcomes could be extrapolated to daily practice. It might therefore be justified to treat selected HER2-positive MBC patients in daily practice with newer treatment options that have shown efficacy in a clinical trial setting.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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